MMR Vaccination, Crohn's Disease and Autism: A Real or Imagined "Stomach ache/Headache?"

Justine H. Passwell MD

Department of Pediatrics, Sheba Medical Center, Tel-Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Israel

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Ever since Edward Jenner's brilliant clinical observation just over 200 years ago that milkmaids were protected from smallpox following vaccination by low virulent cowpox virus, medical science has successfully endeavored to provide increasing numbers of vaccines to prevent infectious disease, particularly in the vulnerable pediatric population. Smallpox is now extinct and routine vaccination is no longer recommended, the fear of poliomyelitis epidemics has also virtually been eliminated, tetanus and diptheria only occur in non-immunized individuals, and remarkable success has recently been achieved with polysaccharide conjugate vaccines for preventing invasive *Haemophilus influenzae* bacterial infection. This is particularly opportune in the light of emerging antibiotic resistance by the common bacterial pathogens. Prevention is better than cure; it is also cost-effective, and the widespread use of vaccines must clearly be hailed as one of the major advances of the past century.

Measles caused by a paramyxovirus is the most transmissible human disease known to date, and in the underprivileged areas of the world still accounts for 10% of global mortality from all causes in children under the age of 5 (approximately 1 million deaths annually) [1]. Measles in a malnourished child is a deadly combination; but even in the western world, including Israel, outbreaks occur when herd immunity wanes, causing significant mortality. In Israel, outbreaks occurred as recently as 1991 and 1994 with approximately 1,000 reported cases and 3–4 deaths in each instance. This is the usual reported mortality rate [Dr. P.E. Slater, Dept. of Epidemiology, Ministry of Health; personal communication].

The immunopathogenesis of disease is now better defined. The virus initially binds to the CD46 receptor, a complement inhibitory protein. Ensuing severe immunosuppression is consequent on deregulation of cell-cycle control proteins, so that lymphocyte proliferation responses are down-regulated; in particular, IL-12 production is reduced and the critical Th1–IFNγ macrophage activation axis is impaired [2–4]. This immunosuppression explains the serious complications of the disease, which includes measles pneumonia, encephalitis and secondary bacterial infection.

Considerable reduction in the incidence of the disease has been achieved by mass immunization with an attenuated virus prepared in chick embryo cultures. The vaccine is now routinely administered at age 12–15 months, together with attenuated mumps and rubella viruses. In recent years, a second booster shot in the early school years has been recommended. This strategy, first demonstrated in the pediatric population of Finland, has reduced outbreaks, boosted waning immunity, and increased the rate of immunity in the vaccinated population [5]. Children between the ages of 6 months and one year are a particularly vulnerable population during outbreaks, since they have lost passive immunity acquired from their mothers' transfer of placental IgG and are not yet capable of mounting an adequate cellular immune response because of their immature immune system. Nevertheless, during an epidemic, immunization even at this early age is recommended [6].

Rubella vaccine is necessary primarily to prevent the devastating syndrome of congenital rubella with deafness, congenital heart disease, eye cataracts, and mental retardation. In Israel, like in Britain, we have learnt from the experience of our North American colleagues that the policy of immunizing only adolescent girls against rubella, rather than the present strategy of immunizing both sexes at an early age to prevent epidemics, was incorrect. The all too familiar past scenarios of public panic during the epidemics of recent years, together with the inability of the medical system to cope with testing pregnant females for the disease, have now been eliminated. The severe consequences of intrauterine infection and the increased rate of elective abortions that occurred during these outbreaks were clearly undesirable. All this is now history. In addition, the complications of mumps infection, such as meningoencephalitis and epididymitis with later compromised fertility, have also been virtually eliminated with this vaccination.

In the present publication, Wakefield and Montgomery [7] reiterate and review their hypothesis previously reported in *The Lancet* that early exposure to measles may be important in the later development of Crohn's disease. Even more dramatic is their suggestion that exposure to MMR vaccine may be associated with a unique, subtle

form of enterocolitis, which subsequently is associated with the development of autism. The evidence for the latter was obtained from a series of 12 children who reported relatively mild gastrointestinal symptoms shortly after MMR vaccination in association with the behavioral changes typical of autistic regression [8]. Usually, it is unlikely that patients with such subtle gastrointestinal symptoms would warrant further investigation apart from clinical follow-up. However, endoscopic, radiological and pathological abnormalities indicative of mild inflammatory changes were reported in these children's bowel specimens. Subtle abnormal histopathology and varied nonspecific immune deficiencies in patients with developmental regression disorders have also been reported by this group, albeit in abstract form. The evidence to prove their hypothesis is limited; yet the public outcry that occurred in Britain following these publications is not surprising and there was indeed some decline in vaccine administration as a result. Extensive rebuttal of this hypothesis has appeared in the medical literature. Carefully documented epidemiological studies in England and Finland have in fact refuted the findings of Wakefield and his co-workers [9–12]. In addition, the initial claim by these authors that measles viral protein was detected in the tissue of Crohn's disease could not be confirmed by more sensitive RT-PCR techniques [13].

In recent years, the pediatric community witnessed a comparable situation, when whole pertussis vaccine was implicated in the etiology of encephalopathy. A causal relationship was difficult, if not impossible, to establish since both disease and vaccination occurred during the same period. Moreover, there was no control group, no experimental model was available, and cerebral pathology was nonspecific. In fact, vaccine damage claims were dismissed in the British courts. What did become clearly apparent was that the decline of vaccine delivery resulted in a marked resurgence of pertussis with considerable infant mortality and morbidity. The vaccine, which was a poor immunogen anyhow, has now been replaced in the United States by combined acellular component vaccines that have fewer local and general side effects. This is unlikely to be the end of this story though, since there is still no consensus as to the most protective immunogens in pertussis. It is noteworthy, however, that pertussis toxin is included in all the licensed vaccines [14,15].

The increased incidence of autism in siblings and the high concordance rates in monozygotic twins indicate that genetic factors are important in the pathogenesis of childhood autism [16]. We are still a long way from proving what other factors, if any, may precipitate this devastating disorder or participate in its pathogenesis. The evidence that MMR is implicated in either Crohn's disease or autism is flimsy at best, and until more definitive evidence and further insights are obtained, the medical community should strongly resist any change in the present vaccination policy. The outcome of decreasing immunization could be disastrous.

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Correspondence: Dr. J.H. Passwell, Chairman, Dept. of Pediatrics, Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel: (972-3) 530 2439; Fax: (972-2) 635 2749; email: jpasswel@post.tau.ac.il.

Under capitalism man exploits man; under socialism the reverse is true.

Polish proverb